



Attorney's Docket No. 7753-113

TECH CENTER 1600/2900

AUG 22 2002

RECEIVED

#25  
8/26/02  
Style  
NE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of )  
Jean-Pierre Robin, et al. ) Group Art Unit 1624  
Application No. 09/270,006 ) Examiner: Venkataraman Balasubramanian  
Filed: March 16, 1999 ) Confirmation No.: 1899  
For: Novel Cephalotaxane Derivatives and )  
Process for Their Preparation )

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

I, Jean-Pierre Robin, hereby declare that:

1. In 1967 I was a graduate in Clinical Biology. In 1970 I was a graduate in Physical Chemistry and Organic Chemistry and received a license in Sciences at Le Mans. In 1970 I was a fellow in Clinical Biochemistry, Hematology, Microbiology, and Parasitology. In 1971 I was a graduate in Macromolecular Chemistry at Le Mans. In 1972 I was a Pharmacist at Tours. In 1975 I was a graduate in Immunology at Nantes. In 1979 I was a doctorate in Sciences, Ph.D., at Le Mans.

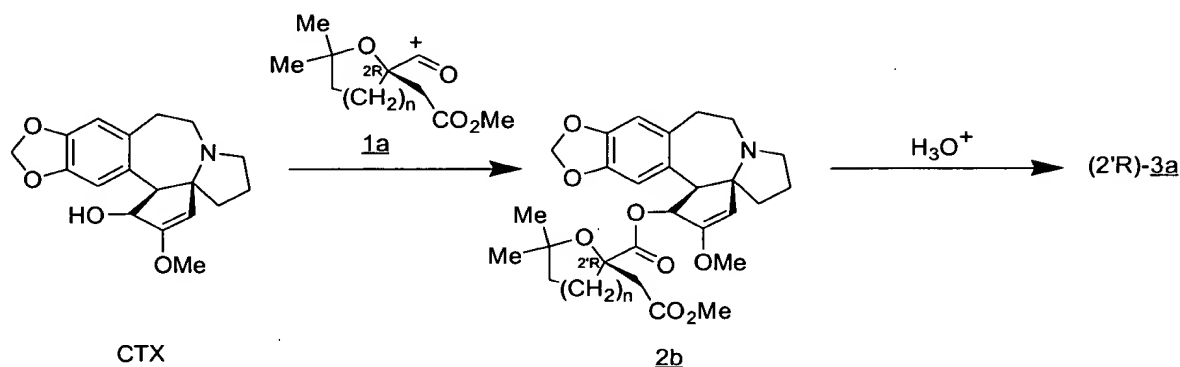
2. I am president, CEO, and major shareholder of Oncopharm Corporation.

3. Attached as Appendix A is my resume.

4. I am familiar with and a named inventor on the above-referenced patent application.

5. As exemplified by scheme 1,

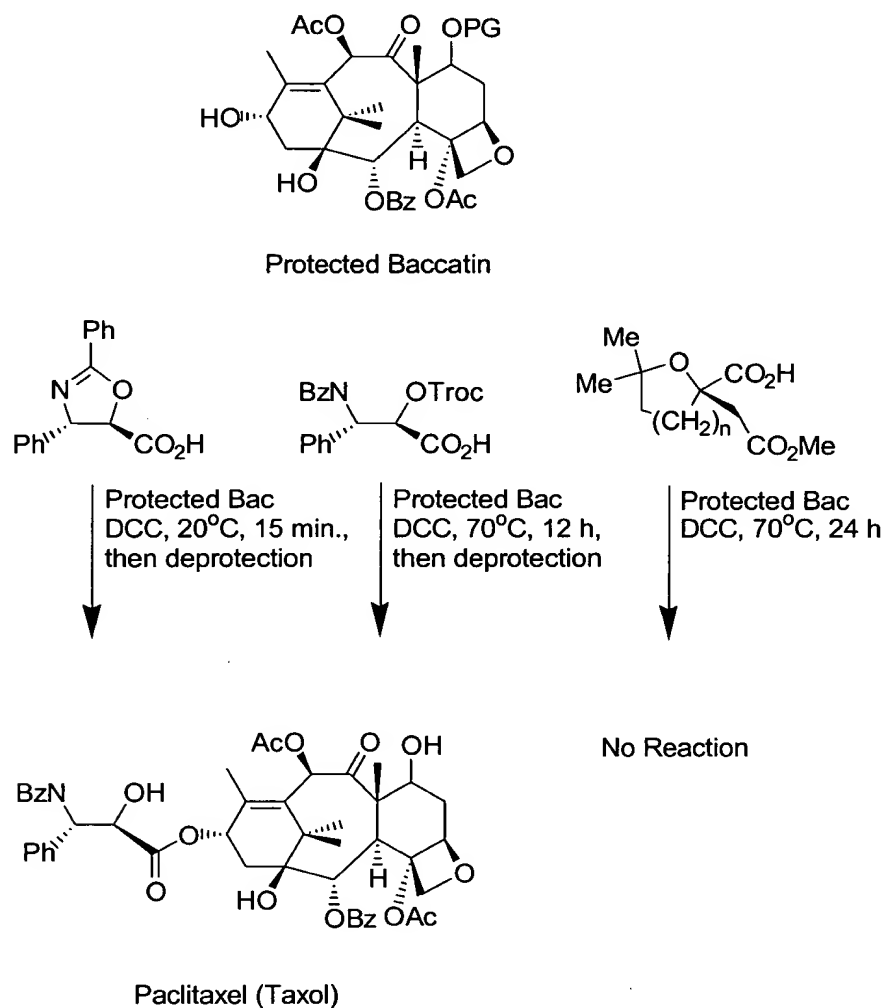
Scheme 1



the present invention consists of the direct esterification of a pentacyclic alkaloid such as cephalotaxine (CTX) by a bulky side-chain precursor such as 1a, in which the backbone and stereochemistry are preformed. Because of the very high steric hindrance of both the side-chain and the alkaloid moieties, the formation of esters such as (2'R)-3a was unexpected, if not impossible, see for example the Hudlicky literature review. Hudlicky, T., et al., *Synthesis of Cephalotaxine Alkaloids*, The Alkaloids, Vol. 51, Chapter 5, 1998, pp. 639-691, Academic Press, Burlington, MA., USA.

6. According to personal experience in paclitaxel semi-synthesis (see scheme 2 below and attached resume), esterification of a hindered alcohol such as protected Baccatin, with a bulky linear side-chain is difficult, and a large contact time and high temperature are necessary.

Scheme 2

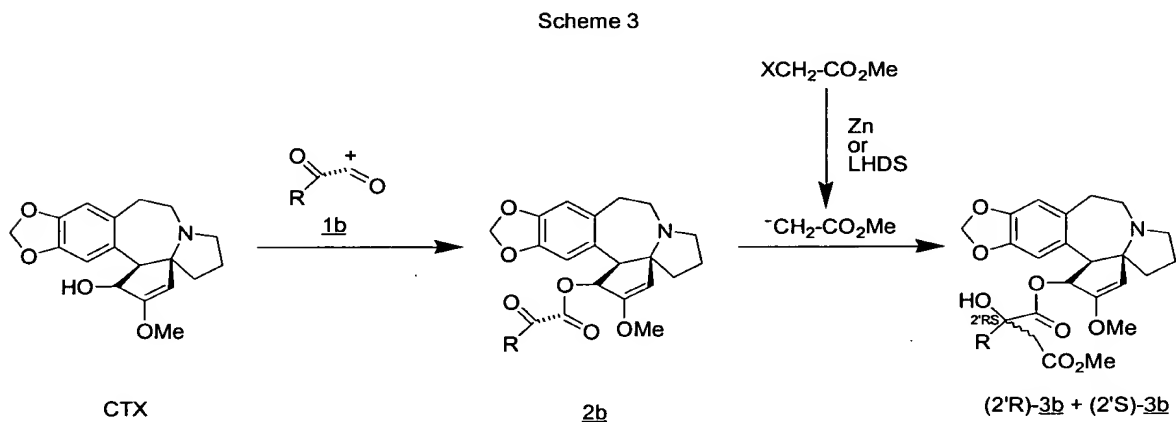


When hindrance is reduced such as in a side-chain in cyclic form, the coupling of the two moieties is greatly facilitated (see scheme 2). However, when the hydroxyl in the alpha position of the carbonyl is free or protected by an excessively bulky protective group, the esterification becomes difficult or impossible even at high temperature.

7. In addition, we experienced that the esterification of protected Baccatin (the precursor of paclitaxel semi-synthesis) by 1a ( $n = 2$ ) failed consistently, whereas a similar cyclic side-chain without a branching in the alpha position easily gave the wanted ester as direct precursor of paclitaxel (Taxol) (see scheme 2 and attached resume). Because the hydroxyl of cephalotaxine is

considered very hindered, the success of the esterification of cephalotaxine by 1a was even further unexpected, a crucial point which shows the inventive aspect of this step.

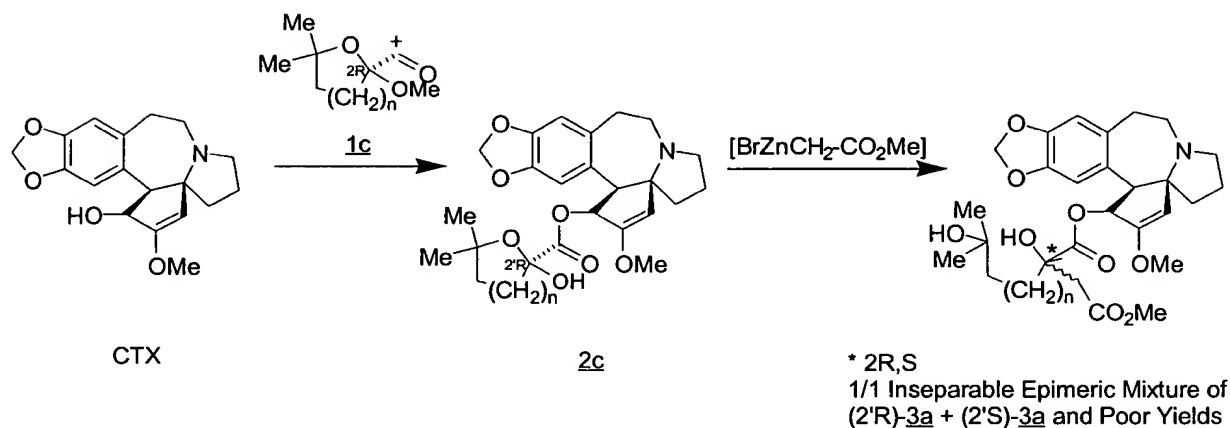
8. As summarized in scheme 3,



and in the Hudlicky recent review, every synthesis described in the literature used an alpha keto-acid (or its acylating form) such as 1b in which R cannot have a free hydroxyl, for the esterification of the hydroxyl of cephalotaxine, to give the alpha-keto ester 2b. Then this keto-ester is submitted to alpha-hydroxylation by the anion of ethyl acetate, generated mostly by a Reformatsky reaction, to give a 1/1 inseparable epimeric mixture of (2'R+2'S)-3b, in poor yield. In summary, the anchorage of the -CH<sub>2</sub>CO<sub>2</sub>Me secondary side-chain after esterification is not able to give a product suitable for pharmaceutical use (but only an inseparable epimeric mixture) and in acceptable environmental conditions related to biodiversity conservation (because Cephalotaxus is a rare and endangered tree and the reaction has a low yield).

10. The Wang II synthesis cited by the examiner, scheme 4,

Scheme 4



circumvents the difficulty of the presence of the free alcohol by including it in a mixed cyclic acetal but does not overcome the inconvenience of the non-stereoselectivity of the post-esterification alpha-hydroxyalkylation, the low yield of the reaction, or the purification of the final epimeric mixture.

11. The description of (2'R)-3a (for  $n = 1$ : anhydro-harringtonine; for  $n = 2$ : anhydro-homoharringtonine) in Wang I, the existence of this intermediate in nature, and finally its retrosynthesis by cyclisation of 2a (the final product of our synthetic scheme) demonstrate that 3a synthesis (in fact retro-synthesis) is chemically possible by a method other than direct esterification from cephalotaxine, but do not provide any argument to predict that either ring opening or direct esterification of cephalotaxine by a hindered side-precursor such as 2a are possible.

12. The sequence as described in Wang II is particularly well commented on in the Hudlicky review. Regarding compound 104, the review mentions page 662: "The exposure of this material to the organozinc reagent derived from methyl bromoacetate and active zinc gave under the conditions of the Reformatsky reaction a mixture of harringtonine and its epimer in a ration of 1:1,1. ... Both groups reported diminished yields of the Reformatsky reaction, because cleavage of the ester under the reaction conditions gave back cephalotaxine. The yields of harringtonine were reported to be 20 and 10%, respectively."

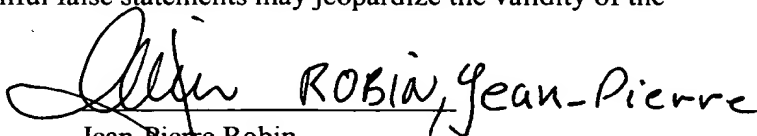
13. Regarding the esterification of cephalotaxine, the Hudlicky review states at page

661: "Most of the synthetic approaches to cephalotaxine esters are concerned [...]. **This is hardly surprising in view of the antitumor activities of these alkaloids. Attempts to prepare these esters by direct esterification of a particular side-chain derivative of cephalotaxine have been uniformly unsuccessful.**"

14. At page 679 of the same review, the author concludes the section related to cephalotaxine ester synthesis by stating: "The message left after nearly 15 years of intensive research in this field has informed synthetic chemists that the problem of esterification of cephalotaxine, the question of steric requirements of side-chain attachment and the overall efficiency of the syntheses were all grossly misjudged at the onsets of their investigations. These problems were not simple and are but partially solved today only because scores of investigators devoted their time to examining every possible detail of a deceptively elementary reaction in organic synthesis, namely, an esterification. ... Of special significance will be the design of syntheses with complete stereocontrol because the separation of isomers, especially the isomers differing in the stereochemistry of side-chain esters, proved extremely tedious and difficult."

15. If the Wang intermediate 3c described in 1978 would allow chemists to predict that harringtonines could be synthesized via intermediates such as 1a and to solve the problem of stereoselective synthesis of harringtonines, it is incomprehensible that these ideas did not appear in the chemist community for several decades. For this reason, we contend that no preceding work indicates that direct esterification of cephalotaxine by an ester bearing a hindered hydrocarbonated branched chain with a preformed asymmetric center in alpha of the carbonyl function was possible and that most of the inconvenience in the existing state of the art, as summarized in recent reviews, was overcome by the present invention.

16. I hereby declare that all statements made herein of our own knowledge are true and that all statements made upon information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under 18 United States Code section 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

  
Jean-Pierre Robin

Date: August 16, 2002

## Robin, Jean-Pierr , Ph.D. : Résumé

Born in Paris on October 25, 1946

5911 Jefferson Blvd., Frederick, MD 21703, The United States  
Tel (301) 271-0460; Fax (301) 271-8788; Cell phone (713) 305-0314

La Groirie Castle 72650 Trangé, France  
Tel/Fax 02 43 88 21 53 ; cell phone 33-611-96-22-43

jprobin@oncopharm.com



1967	Graduate in Clinical Biology	
1970	Graduate in Physical Chemistry	Le Mans
	Graduate in Organic Chemistry	Le Mans
	Licence in Sciences	Le Mans
1970	Fellow in Clinical Biochemistry, Hematology, Microbiology and Parasitology	
1971	Graduate in Macromolecular Chemistry	Le Mans
1972	Pharmacist	Tours
1975	Graduate in Immunology	Nantes
1979	Doctorat in Sciences, Ph.D.	Le Mans

### Member of Academic Societies:

1970	Société Astronomique de France
1982	American Society of Pharmacognosy
1984	American Chemical Society
1996	American Association of Pharmaceutical Scientists
1998	Société Chimique de France
2000	Parenteral Drug Association

From 1972 to now: Successively manager and president of 11 companies and non-profit organizations:

1973 :Drouard Clinical Laboratory: Manager  
 1976 :Lardy and Robin Clinical Biology Laboratory: Manager and Owner  
 1978: Medical Center Clinical Laboratory: Manager  
 1980: Association for the Advancement of Anticancer Chemotherapy: President (non profit organisation)  
 1987: Holdipharm (corporation): President and CEO and major shareholder.  
 1987: Seripharm (corporation): President and CEO and major shareholder.  
 1987: Taxopharm (corporation): President and CEO and major shareholder.  
 1987: Phobos: President and major partner.  
 1996: Paclipharm (corporation): President and CEO and major shareholder.  
 1996: Oncopharm France (corporation) : President and CEO and major shareholder.  
 1996: Paclipharm France and major shareholder.  
 1998: Oncopharm Corporation: President and CEO and major shareholder.

### Know-now in production of chemotherapeutic agents

Production of podophyllotoxin, etoposide and teniposide  
 Production of vincristine  
 Production of daunosamine and doxorubicine  
 Production of cis-platin  
 Production of 10-deacetylbaccatin III, paclitaxel (Taxol), docétaxel (Taxotere)  
 Production of cephalotaxine and homoharringtonine

## AREAS COVERED BY PUBLICATIONS, CORRESPONDING JOURNALS

### Bi I gy, Bi chimistry, Pharmac I gy

*Biochemical and Biophysical Research Communication*  
*Cancer Chemotherapy and Pharmacology*  
*Compte-Rendu de l'Académie des Sciences (Paris)*  
*Feuillets de Biologie*  
*International Journal of Oncology*  
*Journal of Hypertension*  
*Journal of Clinical Immunology*  
*Pharmacological Research Communications*  
*Prostaglandins*

### Applied Organic Chemistry (total synthesis of natural compound)

*Compte-Rendu de l'Académie des Sciences (Paris)*  
*Journal of The Chemical Society, Chemical Communications*  
*Journal of Natural Products*  
*Journal of Organic Chemistry*  
*Tetrahedron*  
*Tetrahedron Letters*

### Fundamental Organic CHEMistry (catalysis, reaction, synthesis)

*Journal of The Chemical Society, Chemical Communications*  
*Journal of Organic Chemistry*  
*Tetrahedron*  
*Tetrahedron Letters*

### Structural Chemistry (Conformational Studies : RX, NMR...)

*Acta Crystallographica*  
*Journal of Natural Products*  
*Tetrahedron*  
*Tetrahedron Letters*

### Medicinal Chemistry (Structure-Activity Relationship )

*Journal of Medicinal Chemistry*  
*Journal of Natural Products*

### Pharmacognosy, Phytochemistry

*Journal of Natural Products*  
*Tetrahedron*  
*Tetrahedron Letters*

### Medecine

*Blood*  
*Hématologie*

**PUBLICATIONS ET BREVETS (Selection)**  
(Unpublished communications to scientific meeting are not included)

**Subcutaneous Homoharringtonine (SQ HHT)\*: 1. Pharmacokinetic Study In Dogs And HHT Determination In Blood Using LC-MS Method. *Blood suppl.* (2001) Abs. # 4409**

**Subcutaneous Homoharringtonine\*\* (SQ HHT): 2. Tolerance In Humans And Case Report Of A Refractory Patient With AML Treated By Very Small Dose Of SQ HHT. *Blood suppl.* (2001) Abs. # 4515**

**Results Of The Clinical Use Of Homoharringtonine (HHT) Combined With Ara-C In The Management Of Advanced Phases Of Chronic Myelogenous Leukemia. *Blood suppl.* (2001) Abs. # 1476**

**Treatment of Chronic Myelogenous leukemia, Resistant or Intolerant to STI571, involving homoharringtonine alone or combined with other agents. Provisional Patent Application; Filing date 09/05/01, No 60/278 673; PCT pending.**

**Highly Purified And Crystalline Form Of Harringtonines, Their Process Of Preparation By Purification Of Crude Alkaloids From Natural, Synthetic Or Semi-Synthetic Sources, Allowing Their Use For Blending In Pharmaceutical Composition Particularly Useful For Treatment Of Cancer In Using Oral Mode Of Administration. Provisional Patent Application; Filing date 03/09/01, No 60/278 673; PCT/FR 02/00992**

**Therapeutic Method Involving Subcutaneous Administration Of Drugs Containing Cephalotaxine Derivatives; US Patent Application; Filing date 03/09/01, No 09/801 751; PCT/FR 02/00853**

**Procédé De Preparation Enantioselective D'adduits De Phenylmethyl-Imino-Cyclo-Alcanes-Substitués Et De 2-Acétoxy-Acrylonitrile, Intermédiaires Dans La Synthèse Énantioselective De La Chaîne Latérale Des Harringtonines. French Patent Application No 0017281, 12/29/2000.**

**New Cephalotaxanes, Their Method Of Preparation And Their Use In Treatment Of Cancers, Leukemias, Parasites Including Thus Resistant To Usual Chemotherapeutic Agents And As Reversal Agents; PCT IB00/01593; US Patent Application 09/710,870 (priority: October 17, 2000).**

**A New Series Of Homoharringtonine (HHT) Analogs Exhibiting A Potent Antileukemic Activity In Vitro; *Blood suppl.* (2000) Abs. #1322.**

**OP5215, A New Semisynthetic Homoharringtonine Derivative, Is Highly Cytotoxic On Multidrug-Resistant Cell Lines; *Blood suppl.* (2000) Abs. #1323.**

**Homoharringtonine ; *Hématologie*, special issue, vol.6, Feb. 2000, 12-14**

**The First Semi-Synthesis of Homoharringtonine Via Anhydrohomoharringtonine From Preformed Chiral Acyl Moiety; *Tetrahedron Lett.* (1999), 40, 2931-4.**

**Novel cephalotaxane Derivatives and Process for their preparation ; US09/270,006; PCT IB99/00491, *Fr. Appl.*, 151 pp. FR 9803492 (Priority : March 20, 1998)**

**Method for selective protection of baccatin derivatives and its application to taxane synthesis; *PCT Int. Appl.*, 31 pp. WO 9724345 A1 970710 WO 96-FR2097 961227.**

Intermediary compounds for the hemisynthesis of taxanes and preparation processes therefore; *PCT Int. Appl.*, 69 pp. WO 9715562 A1 970501 WO 96-FR1676 961025 FR 95-12739 951027.

Preparation of water-soluble epipodophyllotoxins as antitumor agents; *PCT Int. Appl.*, 44 pp. WO 9612727 A1 960502 WO 95-FR1388 951020 FR.

New agents of biaryl oxidative coupling in fluoro acid medium. VI. Application to the synthesis of phenolic bisbenzocyclooctadiene lignans; *Tetrahedron* (1995), 51(5), 1395-404.

Inhibition of tumor necrosis factor-alpha (TNF-alpha.) and interleukin-1 beta (IL-1.beta.) secretion but not IL-6 from activated human peripheral blood monocytes by a new synthetic demethylpodophyllotoxin derivative; *J. Clin. Immunol.* (1994), 14(5), 280-8.

Ruthenium dioxide in fluoro acid medium V. Application to the non phenolic oxidative coupling of diarylbutanes. Conformational studies of cis and trans deoxyschizandrins; *Tetrahedron* (1994), 50(4), 1153-64.

Cytotoxic activity against resistant human tumor cell lines by two synthetic demethylpodophyllotoxin derivatives: a single stereoisomeric change prevents cell death by apoptosis; *Int. J. Oncol.* (1993), 3(6), 1061-6.

Cytotoxic properties of a new synthetic demethylpodophyllotoxin derivative, BN 58705, against human tumor cell lines; *Cancer Chemother. Pharmacol.* (1993), 32(4), 293-300.

Synthesis of non-phenolic bisbenzocyclooctadiene lignan lactones and aporphinic alkaloids, by oxidative coupling with new agents in fluoro acid medium. IV; *Tetrahedron* (1993), 49(26), 5823-30

Ruthenium dioxide in fluoro acid medium. III. Application to the synthesis of aporphinic, homoaporphinic and dibenzazocinic alkaloids. Studies towards the preparation of azafluoranthenic skeleton; *Tetrahedron* (1992), 48(35), 7185-96

Preparation of 2",3",4'-triacyl-4",6"-ethylidene-beta.-D-glucopyranosides as intermediates for anticancer etoposide; *Eur. Pat. Appl.*, 26 pp.

Ruthenium dioxide in fluoro acid medium. II. Application to the formation of steganol skeleton by oxidative phenolic coupling; *Tetrahedron* (1992), 48(5), 819-30

Preparation of etoposide derivatives as intermediates for synthesizing 4'-demethyl-epipodophyllotoxin alkylideneglucosides; *Fr. Demande*, 19 pp. FR 2655047

Ruthenium dioxide in fluoro acid medium. I. A new agent in the biaryl oxidative coupling. Application to the synthesis of non-phenolic bisbenzocyclooctadiene lignan lactones; *Tetrahedron* (1991), 47(23), 3787-804.

Ruthenium catalyst for biaryl coupling; new steganolides; *PCT Int. Appl.*, 40 pp. WO 8705289 A1 870911 WO 87-FR55 870305.

Synthesis of diarylbutanes from cordigerines and reinvestigation of their oxidative couplings in deoxyschizandrins. An unusual formation of phenyltetralin lignans; *Tetrahedron Lett.* (1987), 28(43), 5161-4..

Ruthenium(IV) diacid in fluoro acid medium. An efficient biaryl phenol coupling process, exemplified with a biomimetic access to the skeleton of steganacin from presteganes; *J. Org. Chem.* (1988), 53(1), 224-6.

Ruthenium(IV) tetrakis(trifluoroacetate), a new oxidizing agent. III. An efficient access to the aporphine and homoaporphine skeletons and their structural studies; *Tetrahedron Lett.* (1987), 28(5), 543-6.

Ruthenium(IV) tetrakis(trifluoroacetate), a new oxidizing agent. II. A new access to schizandrin skeleton using biaryl oxidative coupling of cis-substituted butanediols; *Tetrahedron Lett.* (1986), 27(44), 5377-80.

Endogenous lignans - a potential endogenous digitalis; *J. Hypertens.* (1986), 4(Suppl. 5);

Ruthenium(IV) tetrakis(trifluoroacetate), a new catalyst for room-temperature non-phenolic oxidative biaryl coupling. The first total biomimetic synthesis of neo-isostegane; *Tetrahedron Lett.* (1986), 27(16), 1785-8.

Isolation, stereochemical study, and biomimetic synthesis of steganolide A, a new dibenzocyclooctadienolactone lignan of *Steganotaenia araliacea*; *Tetrahedron Lett.* (1986), 27(16), 1781-4.

Steganolides B and C, new lignans analogous to episteganacin and isolated from *Steganotaenia araliacea* Hochst. Carbon-13-proton correlation of steganacin using two-dimensional NMR; *Tetrahedron Lett.* (1986), 27(25), 2871-4.

Inhibition of the erythrocyte sodium-potassium pump by mammalian lignans; *Pharmacol. Res. Commun.* (1986), 18(3), 227-39.

Mammalian lignans: possible involvement in endogenous digitalis activity; *C. R. Acad. Sci., Ser. 3* (1986), 302(12), 443-8.

Preparation, stereochemical study and evaluation of the antileukemic activity of glucosidic (-)-steganol derivatives; *J. Nat. Prod.* (1985), 48(3), 345-56.

Evidence that mammalian lignans show endogenous digitalis-like activities; *Biochem. Biophys. Res. Commun.* (1986), 134(3), 1064-70

Isolation of prestegane B, the first bis(m-hydroxybenzyl)butanolide lignan of plant origin, from *Steganotaenia araliacea* Hochst. Isolation and one-step synthesis of dimethylmatairesin I; *Tetrahedron Lett.* (1984), 25(37), 4127-8

Total synthesis and study of biologically active lignans. III. Application of the  $\alpha$ -hydroxyalkylation of  $\beta$ -benzyl  $\gamma$ -butyrolactones to the preparation of phenyltetralin and bisbenzocyclooctadiene skeletons. First synthesis of picrosteganes, formal synthesis of (+,-)-steganacin; *Tetrahedron* (1984), 40(18), 3509-20

Total synthesis and study of biologically active lignans. 6. Total synthesis of (+,-)-isobetanadin and its analogs; *Tetrahedron* (1984), 40(13), 2529-35.

Neoisostegane, a new bisbenz cyclooctadiene lignan lactone from *Steganotaenia araliacea*; *J. Nat. Prod.* (1984), 47(4), 600-6.

Total synthesis and study of biologically active lignans. Application of the alpha-hydroxyalkylation of beta-benzyl-gamma-butyrolactones to the preparation of phenyltetralin and bisbenz cyclo octadiene skeletons. 5. Total synthesis of (+-)-attenuol; *Tetrahedron* (1983), 39(17), 2795-8.

Total synthesis and study of biologically active lignans. Application of the alpha-hydroxyalkylation of beta-benzyl-gamma-butyrolactones to the preparation of phenyltetralin and bisbenzocyclooctadiene skeletons. 4. Total synthesis of (+-)-steganone and its congeners and synthesis of (+-)-stegane; *Tetrahedron* (1983), 39(17), 2787-94.

Prestegane A, from *Steganotaenia araliacea* Hochst.: the first natural dibenzylbutanolide lignan with a meta-phenol - a short synthesis of cis- and trans-(+)-arctigenin; *Tetrahedron Lett.* (1983), 24(31), 3237-8.

Neoisostegane, a new bisbenzocyclooctadienolactonic lignan from *Steganotaenia araliacea*, Hochst; *Tetrahedron Lett.* (1983), 24(29), 2983-6.

Total synthesis and study of biologically active lignans. II. Application of the alpha-hydroxyalkylation of beta-benzyl-gamma-butyrolactone to the formation of phenyltetralin and bisbenzocyclooctadiene skeletons. Total synthesis of (+-)-podorhizol, (+-)-podorhizone, and (+-)-isodeoxypodophyllotoxin; *Tetrahedron* (1982), 38(24), 3667-71.

Araliangine, a new bisbenzocyclooctadienolactonic lignan from *Steganotaenia araliacea*, Hochst; *Tetrahedron Lett.* (1983), 24(2), 197-200.

Total syntheses of (+-)-isopolygamain, (+-)-isomorelensin, and related aryltetralins; *C. R. Seances Acad. Sci., Ser. 2* (1982), 295(5), 563-6.

Total syntheses and studies of biologically active lignans. I. Application of the Ullmann reaction to the preparation of biaryl precursors of bisbenzocyclooctadiene lignans; *Tetrahedron* (1982), 38(16), 2569-79.

Total synthesis of (+-)-iso-beta-peltatin and its analogs; *Tetrahedron Lett.* (1982), 23(9), 949-52.

Asymmetric total synthesis of the antileukemic lignan precursor (-)-steganone and revision of its absolute configuration; *Tetrahedron Lett.* (1980), 21(28), 2709-12.

8 $\alpha$ -alpha-Hydroxyisopicrostegane; *Acta Crystallogr., Sect. B* (1980), 36(1), 198-200.

Structure-antitubulin activity relationships in steganacin congeners and analogs. Inhibition of tubulin polymerization in vitro by (+-)-isodeoxypodophyllotoxin; *J. Med. Chem.* (1980), 23(5), 546-9.

A stereospecific total synthesis of (+-)-attenuol; *Tetrahedron Lett.* (1979), (16), 1389-92.

A new total synthesis of (+-)-steganone; *Tetrahedron Lett.* (1979), (8), 733-6.

A new route to the bis-benzocyclooctadiene lignan skeleton: total syntheses of (+-)-picrostegan, (+-)-isopicrostegane and (+-)-isostegan; *Tetrahedron Lett.* (1978), (38), 3613-16.

Synthesis of (+-)-picrostegane via intermediate  $\alpha$ -hydroxyalkylation of a  $\beta$ -benzyl  $\gamma$ -butyrolactone; *J. Chem. Soc., Chem. Commun.* (1978), (13), 556-7.

Application of the Ullmann reaction to the synthesis of bulky diaryls, precursors of bisbenzocyclooctadiene lignans. *Tetrahedron Lett.* (1977), (23), 2015-18.

Serum triglyceride determination by a rapid manual micromethod; *Feuill. Biol.* (1974), 15(80), 63-6.

Manual micromethod for total cholesterol assay; *Feuill. Biol.* (1973), 14(74), 107-11.

### **Important inventions or discoveries referenced in handbooks**

Application of Cross Ulmann biaryl coupling reaction and intramolecular alpha-hydroxylation to the synthesis of various natural bridged biaryls.

Application of the Khan-Ingold-Prelog rule of helicity to a new nomenclature of bridged biaryls

First chiral synthesis of steganacin as antitumor agent, and revision of its absolute configuration.

Ruthenium *tetrakis*-trifluoroacetate and related salts of Ruthenium (IV) as novel biaryl coupling agents for the synthesis of biaryllic lignans and alkaloids

Rhenium oxide as novel non-phenolic biaryl coupling agent.

### **References in Handbooks**

#### **Synthetic Organic Reagent (Fieser and Fieser).**

Vol. 8, p 113 and 114

Vol. 13, p 289

Vol. 17, p 304

Vol. 18, p 305

Vol. 18, p 310

#### **Comprehensive Organic Chemistry (Trost)**

Vol 3, p 501, 502, 509, 512, 513

#### **Lignans (Ayres and Loykes**

20 citations.